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Letters to the Editor

ABO blood group and risk of glioma

Age, radiation, and rare hereditary syndromes are the only well-established risk factors for glioma.[1,2] Several retrospective studies in the 1950s and 1960s investigated the relationship between ABO blood group and glioma occurrence; although some reported decreased risk of glioma in patients of group O blood, others found no association.[3,4] Since then, our group showed that O blood type is inversely associated with pancreatic cancer, and non-O type is inversely related to non-melanoma skin cancer.[5,6] We therefore analyzed the association between ABO blood group and risk of glioma in 2 large, prospective cohort studies, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

The methods of both the NHS and the HPFS have been described elsewhere.[5,7] Our analysis included 107 472 participants: 77 373 (72.0%) were women from NHS and 30 099 (28.0%) were men from HPFS (Table 1). The institutional review board at the Brigham and Women's Hospital approved this study.

The 1996 biennial questionnaires in both cohorts asked participants to self-report their ABO blood type (O, A, B, AB, unknown). Although blood type was not confirmed serologically, in a subset of 98 participants from both cohorts, we found a 91% concordance between questionnaire responses and serologic testing.[5] Data for all other covariates were obtained from the 1996 questionnaire, including body mass index (BMI), physical activity, and smoking status. Glioma cases were self-reported on biennial follow-up questionnaires. Deaths (including fatal cases) were identified through the National Death Index, or from next of kin. For all cases, medical records were sought and reviewed. Only cases with confirmed *International Classification of Diseases*, Ninth Revision, Clinical Modification diagnoses of 191.x, indicating malignant neoplasm of the brain, were included in this analysis.

Descriptive statistics were calculated according to ABO blood group. To evaluate differences in risk of glioma by ABO blood type, Cox proportional hazards models were used to calculate age- and multivariable-adjusted hazard ratios (HRs) and 95% CIs. Follow-up time was calculated from the date of return of the 1996 questionnaire to the date of diagnosis, death from another cause, or the end of follow-up (June 2014

Table 1 Baseline characteristics of NHS and HPFS participants reporting ABO blood group in 1996

	NHS (*N* = 77 373)				HPFS (*N* = 30 099)			
	Blood Type				Blood Type			
	O	A	B	AB	O	A	B	AB
Number of participants (%)	33 258 (43.0)	27 524 (35.6)	10 440 (13.5)	6151 (8.0)	12 956 (43.0)	11 130 (37.0)	3709 (12.3)	2304 (7.7)
Baseline characteristics								
Age in 1996, mean (SD)	62.2 (7.1)	62.2 (7.1)	62.2 (7.1)	62.2 (7.1)	63.3 (9.1)	63.3 (9.1)	63.2 (9.0)	63.2 (9.0)
Smoking (%)								
Never smoker	44	45	44	43	48	50	48	48
Past smoker	44	43	44	43	46	44	46	46
Current smoker	13	12	13	13	6	6	6	6
BMI (%)								
<25	43.1	43.4	42.5	44.3	40.6	41.1	41.7	42.7
25–30	34.2	34.3	35.0	33.8	47.3	47.1	46.9	46.8
>30	22.8	22.3	22.6	21.9	12.1	11.8	11.4	10.5
Physical activity quintiles (%)								
Lowest	20.0	19.7	20.0	19.9	20.7	19.4	19.7	21.2
Second	19.9	19.6	20.1	20.3	19.3	20.6	19.8	19.9
Third	19.7	20.3	19.4	19.4	20.0	20.0	20.3	19.0
Fourth	20.4	20.6	20.9	19.9	19.8	20.6	19.7	19.3
Highest	20.2	19.7	19.7	20.5	20.2	19.5	20.5	20.7

Table 2 ABO blood group and risk of adult primary brain malignancy among all participants, NHS participants, and HPFS participants

Blood Type	Total (N=107,472)			NHS (N=77,373)			HPFS (N=30,099)		
		Model 1[a]	Model 2[b]		Model 1[a]	Model 2[b]		Model 1[a]	Model 2[b]
	Events	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Events	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Events	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
O	89	1.00 (ref)	1.00 (ref)	44	1.00 (ref)	1.00 (ref)	45	1.00 (ref)	1.00 (ref)
A	84	1.13 (0.84–1.53)	1.12 (0.83–1.51)	53	1.47 (0.98–2.19)	1.46 (0.98–2.18)	31	0.80 (0.51–1.26)	0.80 (0.50–1.26)
B	24	0.89 (0.57–1.39)	0.90 (0.57–1.41)	16	1.17 (0.66–2.07)	1.17 (0.66–2.07)	8	0.62 (0.29–1.32)	0.63 (0.30–1.33)
AB	23	1.39 (0.88–2.20)	1.41 (0.89–2.24)	13	1.56 (0.84–2.89)	1.57 (0.85–2.92)	10	1.25 (0.63–2.49)	1.27 (0.64–2.53)

NHS=Nurses' Health Study; HPFS=Health Professionals' Follow-up Study.
[a]Adjusted for age (continuous).
[b]Adjusted for age (continuous), cohort (NHS, HPFS, which also adjusts for sex), smoking status (never, past, current), BMI (<25, 25–30, >30), and physical activity (quintiles of metabolic equivalent task hours per week).

for NHS; February 2015 for HPFS), whichever came first. Multivariable models were adjusted for age (continuous), cohort, BMI (kg/m^2; <25, 25–30, >30), physical activity level (metabolic equivalent task [MET] hours per week; sex-specific quintiles), and smoking status (never, past, current). All statistical analyses were performed using the SAS 9.4 statistical package, and all *P*-values were derived from 2-sided tests.

Mean follow-up was 16.1 years, during which we documented 314 incident gliomas among 107 472 participants (NHS: 220, HPFS: 94). Of these, 55% were astrocytoma, 2.2% were oligodendroglioma, 0.9% were ependymoma, 0.6% were mixed glioma, and 40% were not specified. The distribution of blood types was similar across cohorts (Table 1).[5,6]

Age-adjusted models showed no significant difference in risk of glioma in blood group A (HR = 1.11, 95% CI: 0.86–1.42), B (HR = 0.90, 95% CI: 0.62–1.30), or AB (HR = 1.09, 95% CI: 0.71–1.65) compared with group O. The results were materially unchanged after adjusting for cohort, smoking status, BMI, and physical activity, or in subgroup analysis by cohort (Table 2).

In this study of more than 100 000 adults in the United States and nearly 20 years of follow-up, no statistically significant differences in risk of glioma were identified by ABO blood type. To our knowledge, this is the first prospective study of ABO blood type and risk of glioma. Previous reports were mostly small, retrospective analyses of patients undergoing surgery for glioma.[3,4] The results of those studies were mixed, with some reporting higher risk in A-type blood, others reporting higher risk in B-type blood, and still others reporting no association.

These findings suggest that ABO blood group may not play a role in the development of glioma. This is particularly notable in light of recent reports of significant effects of ABO blood type on the incidence of skin and pancreatic malignancies.[5,6] Suggested mechanisms of these altered risks include modification of the immune response through the role of glycoconjugates in intercellular adhesion and membrane signaling.[6–8] This study suggests that the immune response to primary malignancies of the brain may differ from those of cancers at other sites.

Strengths of this study include its prospective design, large sample size, medical record confirmation of outcome, and long follow-up time. Limitations include the modest number of cases, as well as the self-reported nature of ABO blood group, though a validation study showed high concordance between self-report and serologic confirmation.

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References

1. Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. *JAMA*. 2013;310(17):1842–1850.
2. Bondy ML, Scheurer ME, Malmer B, et al.; Brain Tumor Epidemiology Consortium. Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. *Cancer*. 2008;113(7 Suppl):1953–1968.
3. Strang RR, Tovi D, Lopez J. Astrocytomas and the ABO blood groups. *J Med Genet*. 1966;3(4):274–275.
4. Garcia JH, Okazaki H, Aronson SM. Blood-group frequencies and astrocytomata. *J Neurosurg*. 1963;20:397–399.
5. Wolpin BM, Chan AT, Hartge P, et al. ABO blood group and the risk of pancreatic cancer. *J Natl Cancer Inst*. 2009;101(6):424–431.
6. Xie J, Qureshi AA, Li Y, Han J. ABO blood group and incidence of skin cancer. *PLoS One*. 2010;5(8):e11972.
7. Khalili H, Wolpin BM, Huang ES, et al. ABO blood group and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2011;20(5):1017–1020.
8. Wolpin BM, Kraft P, Gross M, et al. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium. *Cancer Res*. 2010;70(3):1015–1023.

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Sex as a biological variable in response to temozolomide

Although a majority of glioblastoma (GBM) patients are males at a ratio of 3 to 2,[1] sex is commonly overlooked as a biological variable in research. In June 2015, the National Institutes of Health recommended the inclusion of both sexes in research studies.[2] Studies investigating response to temozolomide (TMZ) in male versus female patients who have diagnoses of GBM have not been conclusive. Shah et al found female sex to be a prognostic indicator of improved overall survival in a retrospective review of >3300 elderly patients who received combination TMZ and radiotherapy.[3] However, in a second large population review using multivariate analysis, Rusthoven et al did not find a significant difference in response to chemotherapy and radiation combination treatment between elderly male and female patients.[4]

Here we investigated the impact of sex on the therapeutic response in mice bearing intracranial glioma. All animal experiments were approved by and carried out in accordance with The Ohio State University Institutional Animal Care and Use Committee guidelines. Briefly, sibling athymic nude male and female mice bearing intracranial U87ΔEGFR glioma (derived from a male GBM patient[5] and verified by short tandem repeat profiling to match U-87MG [German Collection of Microorganisms and Cell Cultures] at all loci on January 14, 2015) were treated with TMZ at a dose of 25 mg/kg body mass for 5 consecutive days (days 8–12 post tumor cell implantation) via oral gavage. This dosage schedule mimics the human-equivalent TEMODAR cycle of 75 mg/m^2/day for newly diagnosed high-grade glioma.[6] Mice were monitored for tumor-associated luciferase activity to evaluate relative tumor growth (Fig. 1A); survival was also measured (Fig. 1B, red line, male, vs blue line, female). In this model, we did not observe a difference in tumor growth or overall survival in untreated males ($n = 16$) versus females ($n = 18$). Luciferase imaging revealed no significant sex differences in tumor growth on days 6–14 post tumor cell implantation (measured by total flux of luciferase images, average of 5 mice per group, quantification not shown). TMZ-treated males ($n = 30$) trended toward an improved overall survival compared with TMZ-treated females ($n = 30$); however, this trend was not statistically significant ($P = 0.1786$). Males lived to a median of 25.5 days, whereas females lived to a median of 23 days (Fig. 1B, black line, male, vs yellow line, female).

Our findings demonstrate that U87ΔEGFR glioma bearing athymic nude male and female mice exhibit similar tumor growth and therapeutic response to TMZ. Based on this, for future preclinical studies utilizing TMZ, we recommend investigators match the sex of human glioma cell lines to the sex of nude mice in lieu of repeating each cell line in both the sexes.

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